REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of July 18, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim 1 has been amended. Claims 2-38 have been canceled. Claims 39-46 have been withdrawn from consideration as being drawn to non-elected inventions. Claims 1 and 39-46 are pending in the instant application. Claim 1 (as drawn to a biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1) constitutes the elected Group I invention. As later explained, under the heading **Request for Rejoining of Claims Under *Ochiai*** (see page 8), if this claim (claim 1)is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with *Ochiai* is respectfully requested.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendment to claim 1. The amendment was made to more distinctly claim the subject matter Applicants regard as the invention. The claimed biopolymer marker peptide is recited as "isolated" to clarify that the claimed biopolymer marker peptide is indeed patentable subject matter.

Restriction/Election

The Examiner indicates that since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

However, Applicants respectfully remind the Examiner that new claims 39-46 were added in the Response to Restriction Requirement filed on June 9, 2003. At this time, Applicants had received only a written requirement for restriction (mailed on February 5, 2003) and not an action on the merits (see MPEP 810). The action on the merits was not mailed until July 18, 2003.

Request for Rejoining of Claims Under *Ochiai*

Applicants respectfully submit that the Examiner has misinterpreted the reference to the decision in *In re Ochiai* in the Response filed on June 9, 2003. Applicants did not intend for this reference to be considered as an argument for withdrawal of the restriction requirement, but intended the reference to be a request

to rejoin claims 39-46 (withdrawn as being drawn to a non-elected invention) with the claim of the elected invention (claim 1, Group I) **after** the claim of the elected invention is deemed allowable by the Examiner. The request for rejoining under *Ochiai* is reiterated below for the convenience of the Examiner.

The instant application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochiai*. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner enter claims 39-46 in the instant application as being drawn to a non-elected invention and consider joining them (claims 39-46) with claim 1 of the elected invention (Group I) upon the Examiner's determination that claim 1 of the elected invention is allowable, since if the biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Sequence compliance

On page 14 of the Response filed on June 9, 2003, Applicants indicated that the first and last amino acid residues of SEQ ID

NOS:1-3 (shown in parentheses on page 46 of the original disclosure) are added during experimentation for the purpose of protein purification. A more complete explanation of the inclusion of amino acid residues 1 (K) and 19 (K)to SEQ ID NO:1 is presented herein.

The first (K) and last (K) amino acid residues of SEQ ID NO:1 are shown in parentheses in the original disclosure at page 46, line 14. When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NO:1 are predicted residues as disclosed by the use of parentheses. The first and last amino acid residues of SEQ ID NO:1 are disclosed in the specification and the Sequence Listing, however the biopolymer marker peptide identified in patient sera consists of amino acid residues 2-18 of SEQ ID NO:1. The amendments made previously to the claims and specification limiting the marker sequences to specific amino acid residues are made for the purpose of clarification of the use of parentheses only. The claims as previously amended limit the biopolymer marker peptide sequence to amino acid residues 2-18 of SEQ ID NO:1.

Rejections under 35 USC 101

Claim 1, as originally presented, stands rejected under 35 U.S.C. 101 because the claimed invention allegedly is directed to non-statutory subject matter.

The Examiner alleges that the claim fails to include any limitations which would distinguish the claimed polypeptide sequence from those polypeptide sequences which occur in nature.

Claim 1 has been amended to recite an isolated biopolymer marker peptide. As used within the instant specification (at page 20, lines 9-16), the term "isolated"is interpreted to mean "altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original environment or both. A polypeptide, such as that claimed herein (amino acid residues 2-18 of SEQ ID NO:1), naturally present in a living organism is not "isolated", however the same polypeptide separated from the co-existing materials of its natural state is "isolated". It is clear from the methods recited herein that the claimed polypeptide marker (amino acid residues 2-18 of SEQ ID NO:1)is obtained from samples which have been isolated from a patient's body, thus the claimed polypeptide is "isolated" (see page 52, lines 11-14).

Accordingly, it is respectfully submitted that the Applicants have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the

above-rejection under 35 U.S.C. 101 be withdrawn.

Claim 1, as originally presented, also stands rejected under 35 U.S.C. 101 because the claimed invention allegedly is drawn to an invention with no apparent or disclosed specific and substantial credible utility.

The Examiner begins by stating that the instant application provides a description of a peptide. The Examiner then asserts that the instant application does not disclose a specific biological role for this peptide, or its significance to a particular disease, disorder or physiological process which one would wish to manipulate for a desired clinical effect.

Applicants must show that the claimed invention is "useful" for some purpose either explicitly or implicitly (MPEP 2107.01). Claim 1 is drawn to a biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) specifically diagnostic for Alzheimers disease. Clearly, the claimed peptide represents a diagnostic tool for Alzheimers disease. The significance of the claimed peptide to a particular disease (Alzheimers disease) is utilization as a diagnostic tool. Thus, contrary to the Examiner's assertions the instant application does disclose the significance of the claimed peptide to a particular disease state.

The claims particularly point out and distinctly claim that which Applicants regards as the invention (MPEP 608.01(i)). In

other words, the claims define the invention. Claim 1 is drawn to a biopolymer marker peptide diagnostic for a disease state. Thus, the use for the biopolymer marker peptide is indication of a disease state. No where is a specific biological role for the biopolymer marker peptide claimed; nor is any type of manipulation of the biopolymer marker peptide claimed. Applicants are not required to a provide a utility for information that is not claimed. Thus, whether the instant application discloses a specific biological role (or manipulation of) for the claimed peptide is irrelevant to the utility of the claimed invention.

The Examiner alleges that the instant specification fails to provide any information on how to use the disclosed peptide as a marker for Alzheimers disease. The Examiner further alleges that there is no information disclosed in the instant specification which would provide evidence or sound scientific reasoning that the claimed peptide is specifically associated with Alzheimers disease. The Examiner continues to allege that the instant specification fails to provide guidance on how the detection of a biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 in any sample can be used in a diagnosis of Alzheimers disease.

Applicants respectfully disagree with the Examiner's assertions. It is clear that claim 1 recites a specific biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1)

specifically diagnostic for Alzheimers disease. "Diagnostic for Alzheimers disease" explicitly constitutes a specific and substantial utility for the claimed biopolymer marker peptide. The Examiner is reminded that Applicants need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement (see MPEP 2107, II, B (1) (ii)).

The use (utility) of the claimed peptide is for diagnosis of Alzheimers disease. Applicants are not required to explain the disease process in Alzheimers disease; Applicants are only required to show that the claimed peptide is indicative of Alzheimers disease (see MPEP 2165.03). Applicants respectfully submit that the instant specification, including the drawings, clearly supports the credibility of the utility of the claimed peptide.

Applicants provide a general disclosure of the protocols and methods used to isolate and identify the claimed biopolymer marker peptide at pages 37-40 of the instant specification. Pages 40-46 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptide. Furthermore, electrophoretic, mass spectrometric and chromatographic techniques are well-known to those of skill in the art, thus even if specific protocols were not included within the disclosure, one of skill in the art would be familiar with the techniques used and would know how to carry out the protocols in

the instant disclosure. Alternatively, if one of skill in the art did not know exactly how to carry out the protocols in the instant disclosure, one of skill in the art would know where to locate the information in the prior art since the techniques used in the instant disclosure are well-described in the art. Applicants are not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (MPEP 2164.01)).

Applicants clearly teach in the instant specification how the claimed peptide was determined to be diagnostic for Alzheimers disease and further set forth a method which can be followed to determine markers of any disease condition. For example, according to the method of the instant invention; biological samples (types of samples are listed at page 48, lines 5-9 of the instant specification) are obtained from both patients having a disease condition and normal (healthy) patients. The two groups of samples are resolved by polyacrylamide gel electrophoresis. The resulting protein bands appearing from the diseased samples are compared with the protein bands appearing from the normal samples. Bands which differ in some way (down-regulated, up-regulated, present or absent) between the samples are excised from the gel. The bands represent whole proteins or groups of proteins as they are separated from the patient sample. After excision from the gel, the proteins are purified (from the gel) and are subjected to enzymatic

digestion, chromatography, sequencing and identification with mass spectrometric techniques. None of the bands on any of the gels (Figures 1, 3 and 5) correspond directly to the claimed peptides; since these peptides are separated from selected bands which differ between the disease and normal states.

For example, with reference to Figure 1, biological samples were obtained from both Alzheimers patients and patients not suffering from Alzheimers disease. The patients not suffering from Alzheimers disease were age-matched with the Alzheimers patients. A control of pooled normal human serum from healthy patients of various ages was also used (see lane 9 of the gel shown in Figure 1 as read from the left). The two groups of samples and the normal control were resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the diseased samples were compared to the protein bands appearing in the age-matched and normal samples. Protein bands which differed in some way (down-regulated, up-regulated, present or absent) between the samples were excised from the gel. In Figure 1 (DEAE 3 Elution gel), lanes 1-4 (as read from the left) contain biological samples obtained from Alzheimers patients, lanes 5-8 contain biological samples from age-matched patients, lane 9 contains a sample of normal human serum and lane 10 shows the molecular weight standards used for size interpretation. The patient sample numbers are listed at the bottom of the lanes. Two bands (C1 and C3) appeared distinctly and

strongly in a sample obtained from an age-matched patient as compared to a band (C2) of similar size in samples obtained from Alzheimers patients. The decreased presence of the bands (C1 and C3, as compared with C2) in samples obtained from Alzheimers patients represents the down-regulation and/or fragmentation of the proteins (including the claimed peptide) contained in these bands in Alzheimers disease. Thus, one of skill in the art would recognize from the protocols and figures disclosed in the instant specification that, in this case, the down-regulation of the claimed biopolymer marker peptide is indicative of Alzheimers disease. Accordingly, Applicants respectfully submit that the instant specification provides sufficient guidance on how to use the claimed biopolymer marker peptide as an indicator of Alzheimers disease.

With regard to the excision of protein bands from the gel, no conventional control is applied(as explained in the Declaration filed herewith). Both samples from diseased patients and samples from healthy patients are separated by polyacrylamide gel electrophoresis. The bands which differ between healthy and diseased are excised. A determination of up-regulation, down-regulation or absence/presence of the proteins isolated from the bands is assessed by sample in which they appear, for example, the claimed peptide fragment was excised from a band which exhibited decreased expression in the diseased samples as compared with the

expression in the age-matched samples. Thus, this is considered to be down-regulation of the claimed peptide in the disease state.

A Declaration Under 37 CFR 1.132 is submitted herewith in order to clarify the use of controls in the experiments disclosed in the instant specification.

The Examiner further asserts that the specification fails to explain the relationship between the claimed biolpolymer marker peptide and a particular disease state. The Examiner questions "Is the up or down regulation of the marker relative to the categorization of the disease state?" and "Is the presence or absence of the peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 indicative of a disease?". The Examiner asserts that the instant specification does not provide answers to these questions and thus undue experimentation is required to answer these questions.

Applicants respectfully disagree with the Examiner's position. On page 5, lines 12-22 of the instant specification, states that the present inventors do not attempt to develop a reference of "normal" but rather strive to specify particular markers whose presence, absence or relative strength/concentration in disease vs. normal is diagnostic of at least one specific disease state or whose up-regulation or down-regulation is predictive of at least one specific disease state. The relationship is observed from a comparison of diseased spectra to normal spectra or a comparison

of protein bands appearing in the diseased sample to protein bands appearing in the normal sample (protein bands as resolved by polyacrylamide gel electrophoresis). This is a simple method of analysis that requires identification of differences in the spectra(or protein bands) of the disease state versus the spectra (or protein bands) of the non-diseased state. Such simple observation does not require "undue experimentation". Thus, the instant specification clearly explains the relationship between the claimed biopolymer marker peptide and Alzheimers disease and further teaches one of skill in the art how to determine if a marker is indicative of a disease state.

The Examiner provides references (Clark *et al.* Archives of Neurology 50:1164-1172 1993 and Motter *et al.* Annals of Neurology 38(4):643-647 1995)which she asserts indicate that it is well-known in the art that a diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy.

The first thing noted about the references is the publication dates; each article was published more than five years prior to the date of Applicants' invention. Theories and standards in biotechnology and medicine change quickly over time due to research advancements and especially change over a five year period. Thus, these references are not considered to accurately assess the state of the art at the time of the Applicants' invention.

Even if these references were contemporary to the state of the

art at the time of the invention, they remain insufficient to support the Examiner's position on the enablement of the instant invention. These references may state that the diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy; but these references do not state or suggest that these will be the only effective means for the diagnosis of Alzheimers disease ever to be used. The instant invention provides improved alternative means for the diagnosis of Alzheimers disease. It is clear from the experiments described in the specification that the instant inventors have developed a method that can provide a simple alternative to the traditional diagnosis of Alzheimers disease, which when applied can lead to earlier diagnosis and thus more effective treatment and an improvement of the quality of life for patients. Thus, for the reasons discussed in the above two paragraphs, the cited references are not deemed relevant to support the Examiner's position.

The Examiner further asserts that the specification fails to disclose any specific information regarding the data presented in Figures 1-6, such as, description of a sample, the representative number of samples, description of control samples and a method of evaluation of the bands displayed in the figures which leads to a conclusion that they are indicative of Alzheimers disease. The Examiner additionally asserts that a skilled artisan would have to resort to substantial amounts of undue experimentation to discover

how to use the claimed biopolymer marker peptide in prediction of Alzheimers disease; such experimentation including determination if the marker is absent or present or strongly present in a normal individual, or is up-or down-regulated in disease.

Applicants respectfully submit that the assertions of the Examiner presented in the paragraph immediately prior to the instant paragraph were addressed previously at pages 15-18 of the instant Response.

The Examiner asserts that the Declaration of Lander under 37 CFR 1.132 filed on June 9, 2003 is insufficient to overcome the rejection of claim 1 because it presents additional information that the claimed peptide is not in normal human serum, such diagnostic relationship does not appear to be taught by the specification as originally filed. 35 USC 101 clearly states that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. The fact that Applicant submits additional data resulted from further experimentation to support the claimed invention, confirms that the instant invention was not complete as filed, and, therefore, clearly lacks utility in currently available form.

The Examiner concludes that to employ a peptide of the instant invention as a marker for Alzheimers disease would clearly be using it as the object of further research, which has been determined by

the courts to be a utility, which alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the claimed peptide in the currently available form, the instant invention is incomplete, and therefore, does not meet the requirements of 35 USC 101.

Applicants respectfully disagree with the Examiner's position. No where is it stated that the Declaration filed on June 9, 2003 presents new or "additional information"; the Examiner appears to have come to this conclusion by assumption. The data presented in the Declaration filed on June 9, 2003 was derived from data collected during the original experimentation. Samples from normal human serum are clearly presented in lanes 9 of Figures 1, 3 and 5 which were presented at the time of filing of the instant application. Thus, Applicants respectfully submit that the instant invention was complete at the time of filing and furthermore, that the peptide of the instant invention is not presented as an object of further research.

The claimed biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is diagnostic for Alzheimers disease. This is the credible "real world" use for the claimed peptide, which is supported by the instant specification as indicated by the above discussion. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claim 1, as originally presented, stands rejected under 35 U.S.C. 112, first paragraph since the claimed invention allegedly is not supported by either a clear asserted utility or a well established utility for the reasons set forth under the 101 rejection (second 101), one skilled in the art would clearly not know how to use the claimed invention.

As clarified in the above discussion (second rejection under 35 U.S.C. 101), the claimed invention is supported by a clear, asserted utility. The claimed biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is diagnostic for Alzheimers disease; this statement represents a clear, asserted utility that is supported by the instant specification (clarified in the above-discussion under the second 101 rejection).

In light of this utility, Applicants assert that one of ordinary skill in the art when reviewing the instant specification would recognize how to use the claimed biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) as a marker for Alzheimers disease. Thus, Applicants respectfully request that this rejection under 35 U.S.C. 112, first paragraph now be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claim 1, as originally presented, stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 1 is vague and ambiguous because it is not clear what limitation the recitation "diagnostic for Alzheimers disease" adds to the claimed subject matter.

Applicants respectfully disagree with the Examiner's assertions. The words of a claim must be given their "plain meaning" unless they are defined in the specification (see MPEP 2111.01). According to Webster's Third New International Dictionary; the term "diagnostic" means "serving to distinguish, determine or identify". The term "diagnostic" is used in the instant specification at page 5, line 16 wherein it refers to a biopolymer marker that is diagnostic of at least one specific disease state. It is clear from this context that the term "diagnostic" means to identify a particular disease state. This context falls within the "plain meaning" of the term "diagnostic". "Plain meaning" refers to the meaning given to the term by those of ordinary skill in the art (see MPEP 2111.01). Applicants respectfully submit that one of ordinary skill in the medical arts would recognize that "diagnostic" refers to an entity which identifies a particular disease. Thus, it is clear that claim 1 recites a biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 which identifies Alzheimers disease.

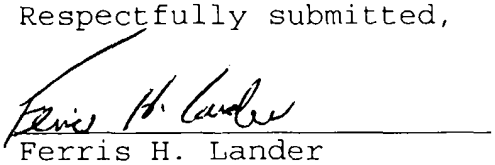
Accordingly, applicants have now clarified the metes and

bounds of the claim and respectfully request that the above-discussed rejection under 35 U.S.C. 112, second paragraph be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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